



Withania somnifera

Introduction

Withania somnifera, also known as ashwagandha, Indian ginseng, and winter cherry, has been an important herb in the Ayurvedic and indigenous medical systems

for over 3000 years. Historically, the plant has been used as an aphrodisiac, liver tonic, anti-inflammatory agent, astringent, and more recently to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia. Clinical trials and animal research support the use of ashwagandha for anxiety, cognitive and neurological disorders, inflammation, and Parkinson's disease. Ashwagandha's chemopreventive properties make it a potentially useful adjunct for patients undergoing radiation and chemotherapy. Ashwagandha is also used therapeutically as an adaptogen for patients with nervous exhaustion, insomnia, and debility due to stress, and as an immune stimulant in patients with low white blood cell counts.

Description

Ashwagandha is a small, woody shrub in the Solanaceae family that grows about two feet in height. It can be found growing in Africa, the Mediterranean, and India. As a result of this wide growing range, there are considerable morphological and chemotypical variations in terms of local species. However, the primary alkaloids of both the wild and the cultivated species appear to be the same. The roots are the main portion of the plant used therapeutically.

The bright red fruit is harvested in the late fall and seeds are dried for planting in the following spring. The berries have been shown to have an emetic effect.

Active Constituents

The major biochemical constituents of ashwagandha root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides.¹ At present, 12 alkaloids, 35 withanolides, and several sitoindosides from this plant have been isolated and studied. A sitoindoside is a withanolide containing a glucose molecule at carbon 27. Much of ashwagandha's pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D.

Mechanisms of Action

The withanolides serve as important hormone precursors that can convert into human physiologic hormones as needed. Ashwagandha is thought to be amphoteric; i.e., it can help regulate important physiologic processes. The theory is that when there is an excess of a certain hormone, the plant-based hormone precursor occupies cell membrane receptor sites so the actual hormone cannot attach and exert its effect. If

the hormone level is low, the plant-based hormone exerts a small effect. Ashwagandha is also considered to be an adaptogen, facilitating the ability to withstand stressors, and has antioxidant properties as well. Other studies have shown ashwagandha to have an immunostimulatory effect.

Clinical Indications

Anti-Aging

In a double-blind clinical trial, ashwagandha was tested in a group of 101 healthy males, 50-59 years old, at a dosage of 3 grams daily for one year. A significant improvement in hemoglobin, red blood cell count, hair melanin, and seated stature was observed. Serum cholesterol decreased and nail calcium was preserved. Erythrocyte sedimentation rate decreased significantly and 71.4 percent reported improvement in sexual performance.²

Immunomodulation and Hematopoiesis

A series of animal studies show ashwagandha to have profound effects on the hematopoietic system, acting as an immunoregulator and a chemoprotective agent.^{3,4} In a mouse study, administration of a powdered root extract from ashwagandha was found to enhance total white blood cell count. In addition, this extract inhibited delayed-type hypersensitivity reactions and enhanced phagocytic activity of macrophages when compared to a control group.⁵ Recent research suggests a possible mechanism behind the increased cytotoxic effect of macrophages exposed to *W. somnifera* extracts.⁶ Nitric oxide has been determined to have a significant effect on macrophage cytotoxicity against microorganisms and tumor cells. Iuvone et al demonstrated *Withania somnifera* increased NO production in mouse macrophages in a concentration-dependent manner. This effect was attributed to increased production of inducible nitric oxide synthase, an enzyme generated in response to inflammatory mediators and known to inhibit the growth of many pathogens.⁷

Ashwagandha exhibited stimulatory effects, both *in vitro* and *in vivo*, on the generation

of cytotoxic T lymphocytes, and demonstrated the potential to reduce tumor growth.⁸ The chemopreventive effect was demonstrated in a study of ashwagandha root extract on induced skin cancer in Swiss albino mice given ashwagandha before and during exposure to the skin cancer-causing agent 7,12-dimethylbenz[a]anthracene. A significant decrease in incidence and average number of skin lesions was demonstrated compared to the control group. Additionally, levels of reduced glutathione, superoxide dismutase, catalase, and glutathione peroxidase in the exposed tissue returned to near normal values following administration of the extract. The chemopreventive activity is thought to be due in part to the antioxidant/free radical scavenging activity of the extract.⁹

An *in vitro* study showed withanolides from *Withania somnifera* inhibited growth in human breast, central nervous system, lung, and colon cancer cell lines comparable to doxorubicin. Withaferin A more effectively inhibited growth of breast and colon cancer cell lines than did doxorubicin. These results suggest *Withania somnifera* extracts may prevent or inhibit tumor growth in cancer patients, and suggest a potential for development of new chemotherapeutic agents.¹⁰

Anxiety and Depression

In an animal study assessing the anxiolytic and antidepressive actions of ashwagandha compared to commonly prescribed pharmaceuticals, an extract of the root was administered orally to rats once daily for five days. The results were compared to a group administered the benzodiazepine lorazepam for anxiolytic activity, and the tricyclic antidepressant imipramine for antidepressant investigation. Both the ashwagandha group and the lorazepam group demonstrated reduced brain levels of a marker of clinical anxiety. Ashwagandha also exhibited an antidepressant effect comparable to that induced by imipramine in the forced swim-induced “behavioral despair” and “learned helplessness” tests.¹¹ Other similar studies confirm these results, lending support to the use of ashwagandha as an antistress adaptogen.¹²⁻¹⁵

Chronic Stress

Chronic stress (CS) can result in a number of adverse physiologic conditions including cognitive deficit, immunosuppression, sexual dysfunction, gastric ulceration, irregularities in glucose homeostasis, and changes in plasma corticosterone levels. In a rat model of chronic stress *Withania somnifera* and *Panax ginseng* extracts were compared for their ability to attenuate some effects of chronic stress. Both botanicals were able to decrease the number and severity of CS-induced ulcers, reverse CS-induced inhibition of male sexual behavior, and inhibit the adverse effects of CS on retention of learned tasks. Both botanicals also reversed CS-induced immunosuppression, but only the *Withania* extract increased peritoneal macrophage activity in the rats. The activity of the *Withania* extract was approximately equal to the activity of the *Panax ginseng* extract. *Withania somnifera*, however, has an advantage over *Panax ginseng* in that it does not appear to result in ginseng-abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension, and insomnia.¹⁶

Cardiovascular Protection

Hypoglycemic, diuretic, and hypocholesterolemic effects of ashwagandha root were assessed in human subjects, in which six type 2 diabetes mellitus subjects and six mildly hypercholesterolemic subjects were treated with a powder extract for 30 days. A decrease in blood glucose comparable to that of an oral hypoglycemic drug was observed. Significant increases in urine sodium, urine volume, and decreases in serum cholesterol, triglycerides, and low-density lipoproteins were also seen.¹⁷

Hypothyroidism

Animal studies reveal ashwagandha has a thyrotropic effect.^{18,19} An aqueous extract of dried *Withania* root was given to mice via gastric intubation at a dose of 1.4 g/kg body weight daily for 20 days. Serum was collected at the end of the 20-day period and analyzed for T3 and T4 concentrations, and lipid peroxidation was measured in liver homogenate via antioxidant enzyme activity. Sig-

nificant increases in serum T4 were observed, indicating the plant has a stimulatory effect at the glandular level. No changes in T3 levels were observed. *Withania* may also stimulate thyroid activity indirectly, via its effect on cellular antioxidant systems. *Withania* extract significantly decreased lipid peroxidation in the liver homogenate and significantly increased catalase activity, promoting scavenging of free radicals that can cause cellular damage. These results indicate ashwagandha may be a useful botanical in treating hypothyroidism.¹⁸

Other Therapeutic Considerations

Studies show ashwagandha to be effective in the treatment of osteoarthritis,²⁰ inflammation,^{21,22} stroke,²³ and tardive dyskinesia.²⁴ Studies also reveal ashwagandha to be a potential antimicrobial agent, with antifungal activity^{25,26} and moderate antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.²⁷

Drug-Botanical Interactions

There are anecdotal reports that ashwagandha may potentiate the effects of barbiturates; therefore, caution should be used if taking this combination.

Side Effects and Toxicity

Ashwagandha is generally safe when taken in the prescribed dosage range.²⁸ Large doses have been shown to cause gastrointestinal upset, diarrhea, and vomiting.

Dosage

A typical dose of ashwagandha is 3-6 grams daily of the dried root, 300-500 mg of an extract standardized to contain 1.5 percent withanolides, or 6-12 ml of a 1:2 fluid extract per day.

Warnings and Contraindications

Large doses of ashwagandha may possess abortifacient properties; therefore, it should not be taken during pregnancy. Since ashwagandha acts as a mild central nervous system depressant, pa-

tients should avoid alcohol, sedatives, and other anxiolytics while taking ashwagandha.

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